CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

FABRICATION AND IN-VITRO CHARACTERIZATION OF TRANSDERMAL MATRIX PATCH OF KETOPROFEN FOR TRANSDERMAL THERAPEUTIC SYSTEM

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Abstract:

Objective: *The objective of research work was to improve the permeability of Ketoprofen and to provide controlled release of drug to provide maximum effective concentration.*

Experimental work: *Transdermal drug delivery systems are polymeric patches containing dissolved or dispersed drugs that deliver therapeutic agents at a constant rate to the human skin. Matrix type transdermal patches containing Ketoprofen were prepared by solvent casting method employing aluminium foil method. Polyethylene glycol (PEG) 400 was used as plasticizer and Dimethyl sulfoxide (DMSO) was used as penetration enhancer. Polymers were selected on the basis of the their adhering and non-toxic property.*

Result and discussion *Drug polymer interactions determine by FTIR and standard calibration curve of Ketoprofen were determine by using UV estimation. Transdermal patch was prepared by using HPMC K-4 M: PVP K-30, HPMC K-15 M: PVP K-30, HPMC K-100 M: PVP K-30, Eudragit RS-100:PVP K-30 showed good physical properties. All prepared formulations indicated good physical stability. In-vitro drug permeation studies of formulations were performed by using Franz diffusion cells using abdomen skin of Wistar albino rat. Result, showed best in-vitro skin permeation through rat skin (Wistar albino rat) as compared to all other formulations prepared with hydrophilic polymer containing permeation enhancer. The permeability of Ketoprofen was increased with increase in PVP content. The burst effect due to the incorporation of PVP was because of the rapid dissolution of the surface hydrophilic drug which gets swell and thus leads to the decrease of mean diffusional path length of the drug molecules to permeate into dissolution medium and higher permeation rates.*

Conclusion: *It was observed that the formulation containing HPMC K-4 M: PVP K-30 (2:3) showed ideal higuchi release kinetics.*

Key words: *Trasdermal drug delivery system, Polymers, Ketoprofen, Matrix type, Permiation.*

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Please cite this article in press as Bhumi Patel and Chainesh Shah, ***Fabrication and In-Vitro Characterization of Transdermal Matrix Patch of Ketoprofen for Transdermal Therapeutic System****, Indo Am. J. P. Sci, 2016; 3(9).*

INTRODUCTION:

Transdermal patches are designed to provide a delivery of the drug substance(s) through the skin, principally by diffusion, resulting in a defined rate and extent of systemic delivery of drug substance [1]. It deliver the drug substance(s) through the intact skin, resulting in a prolonged sustained and adequately constant systemic absorption rate with increased bioavaibility with reduced dose frequency. It provides prolong action of drug with low biological half life's [2].

Ketoprofen is a potent non-steroidal anti inflammatory drug. It is BCS class-II drug having low solubility in acidic medium and high permeability. Ketoprofen is a potent NSAID with BCS Class-II drug having low solubility and high permeability. It has a low biological half life of 1.5-2.0 hrs [3]. Hence it requires a controlled formulation to provide drug release at predetermined rate. It is highly metabolized drug when taken as oral administration and having many gastric side effects [4,5]. Transdermal delivery provides controlled, constant administration of the drug and also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation. Matrix system provides a uniform release for sustained release and easy to manufacture. Ketoprofen is applied as patch provides a constant peak plasma drug concentrations that is used in treatment of post and during operation and sports injuries [6,7].

MATERIALS AND METHODOLOGY:

Materials:

Ketoprofen was a kind gift from Dolphin Pharma PVT LTD., Surat. PVP K-30, PEG-400 & DMSO were kind gifts from Sulab, Bardoli. HPMC K-4, K-15, K-100 and Eudragit RS 100 were purchased from Colorcon Asia pvt, ltd, Goa. Other reagents were of analytical-reagent grade and purchased from the local market. Water was deionized and double distilled.

Drug-Polymer compatibility study by FT-IR spectroscopy [8]:

IR spectroscopy was conducted using a FTIR Spectrophotometer (FTIR-8700, shimadzu, USA) and the spectrum was recorded in the wavelength region of 400–4000 cm^{-1}. The procedure consisted of dispersing a sample (drug alone and mixture of drug and polymer) in KBr and compressing into discs by applying a pressure of 5 t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded. All spectra were collected as an average of three scans at a resolution of 2 cm^{-1}.

Determination of Partition co-efficient [8]

Partition co-efficient of Ketoprofen was determined by saturating 10ml of n-octanol with 10ml phosphate buffer 7.4 in separating funnel for 24 hours.10mg of drug added into separating funnel and intermediate shaking was done for 4 hours. Two solvent layers were separated through separating funnel and the amount of Ketoprofen dissolved in each phase was determined spectrophotometrically at 264nm against reagent blank prepared in the same manner on a U.V-visible spectrophotometer.

Preliminary solvent selection and Optimization of Plasticizer Concentration

Preliminary solvent system:

Film forming solutions were prepared by adding each of the polymer to the different ratios of various solvent mixtures (S1, S2, S3 and S4) and the each solution was stirred for about 30 minutes to ensure complete dissolution of the polymer. The required amount of plasticizer was added to polymer dispersion. The solution was kept in undisturbed condition till the entrapped air bubbles were removed. The solution was casted in a glass Petri dish having diameter of 8.5 cm to form 0.3-0.5 mm thick transdermal patch, and was dried at room temperature. The Petri dishes were put on the leveled surface during drying to avoid variation in the thickness. It was left for approximately 24 hours to dry at room temperature.

Table 1: Different ratios of organic solvents

Code	Solvents	Ratio
1	Methanol: Dichloromethane	1:1
2	Methanol: Dichloromethane	1:2
3	Methanol: Chloroform	1:1
4	**Methanol: Water**	**1:1**

Preliminary screening of Polymer and plasticizer concentration optimization:

It is necessary to find out the minimum amount of polymer provides a elegant patch with proper physic-chemical properties.

Dose of drug and loading drug calculation for transdermal application:

Dose of drug that is placed in a fixed area (2*2 cm^2) can be calculated by the following equation.

$$\text{Dose of drug} = \frac{\text{Oral Dose of drug} \times \text{Oral bioavability}}{\text{Body suraface area}}$$

Where

Oral dose of drug (Ketoprofen) =100 mg

Oral bioavability = 70%

Body surface area = 1.73 cm^2

Drug loading calculation for fabrication of transdermal patch:
As on the basis of dose calculation, the fixed required amount of drug needs to be incorporated in a fixed area of (2*2 cm^2). So the total amount of drug need to be incorporated in total surface area of petri-plate should be calculated.

Formulation of Transdermal matrix patch of Ketoprofen by Solvent casting method [9,10,11]:
The solvent casting method was used for the preparation of the matrix type of TDDS. Polymer blends were taken in varying ratios to form a homogenous matrix system (a total 400 mg polymer). The required amount of plasticizer was added to polymer dispersion. Drug was dissolved in organic solvent then added into polymeric solution with constant stirring for 30 minutes with adequate clarity and mixed in above dispersion. The solution was kept in undisturbed condition till the entrapped air bubbles were removed. The solution was casted in a glass Petri dish having diameter of 5.23 cm to form 0.3- 0.5 mm thick TDDS, and was dried at room temperature. The Petri dish was put on the leveled surface during drying to avoid variation in the thickness. It was approximately 6 hours to dry at 60˚c temperature. The dried TDDS was carefully removed from the plate and was cut into size required for testing. The formulations was stored in airtight plastic bags till after placing aluminum foil as backing layer for further use and stored in desiccators.

Characterization of Developed Transdermal Matrix Patch 8-26]:
Physico-chemical evaluation
Thickness of Patch [12,13]
The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight Uniformity [8,14]
A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content
A specified area (2*2 cm^2) of patch was dissolved in a 5 ml of acetone and the make up the volume up to 10 ml. Then the solution was filtered through a Whatman® filter paper and analyzed through UV-Spectrophotometer at 264nm.

Folding Endurance [15]
This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

Tensile strength [14,15,16]
The tensile strength was determined by using a modified pulley system. It contains two clamps, one was fixed and other was movable. The strip of the patch (2*2 cm^2) was cut and set between these two clamps. Weight was gradually increased on the pan, so as to increase the pulling force till the patch broke. The force required to break the film was consider as a tensile strength (kg/cm^2).
The tensile strength was determined by the following equation.

$$\text{Tensile strength} = \frac{F}{a * b\,(1+\frac{L}{I})}$$

Where F = Force required to break
a =Width of film
b =Thickness of film
L= Length of film
I = elongation of film at break point

Percentage Elongation break test:
The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula.

$$\text{Elongation percentage} = \frac{L1-L2}{L2} \times 100$$

Where, **L1** = final length of each strip and
L2 = initial length of each strip.

Moisture content [17]
The patches were weighed individually and kept in a desiccator containing activated silica/ Sodium hydroxide pellets at room temperature for 24 hrs. The individual patches were weighed repeatedly until a constant weight was achieved. It can be calculated by the following equation.

$$\text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} * 100$$

Moisture uptake [17]
The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions.
The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula
.

$$\text{Moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} * 100$$

Flatness
Three longitudinal strips are to be cut from each film at different portion like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining percent constriction, with 0%

constriction equivalent to 100% flatness.

Swelling index [8-11]

The polymeric film was weighed and put in a Petri dish containing 10 ml of double distilled water and were allowed to imbibe. Increase in the weight of the polymeric film was determined at preset time intervals. until a constant weight was observed.

The degree of swelling index was calculated using the formula.

$$\text{Swelling index} = \frac{Wt - Wo}{Wo} * 100$$

Where

Wo =Initial weight of patch at zero time

Wt = Final weight of Patch at t time.

Adhesive study evaluation

Shear Adhesion test [16,17]

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of cross linking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

***In*-vitro Permeation study**

An *in*-vitro permeation study can be carried out by using diffusion cell receptor compartment capacity of 12 ml. The excised cellophane paper was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer.

Flux and Permeability coefficient [17]

The flux (mg cm^{-2} hr^{-1}) of Ketoprofen was calculated from the slope of the plot of the cumulative amount of Ketoprofen permeated per cm^2 of skin at steady state against the time using linear regression analysis.

The steady state permeability coefficient (Kp) of the drug through rat epidermis was calculated by using the following equation.

$$\mathbf{Kp} = \frac{J}{C}$$

Where J = the flux

C = the concentration of Ketoprofen in the patch.

Ex-vivo Permeation study

An ex-vitro permeation study can be carried out by using diffusion cell receptor compartment capacity of 12 ml. The excised skin of Wister albino rats were was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer.

Kinetic analysis of release data [8]

Zero Order Release

Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs and other delivery systems. In its simplest form, zero order release can be represented as

$$\mathbf{Q = K_0 t}$$

Where Q = the amount of drug release at time t,

K0 = the Zero order release constant

t = the time required for drug release

First Order Release Equation

First order dependence on the concentration gradient (i.e. Cs - Ct) between the static liquid layer next to the solid surface and the bulk liquid. Noyes and Whitney explained their dissolution data using a concept similar to that used for the diffusion model. These considerations relate to conditions in which there is no change in the shape of the solid during the dissolution process (i.e. the surface area remains constant). However, for pharmaceutical tablets, disintegration occurs during the dissolution process and the surface area generated therefore varies with time.

The plot made: log cumulative of % drug remaining vs. time (first order kinetic model).

$$\mathbf{\ln (100-Q) = \ln Q_0 - k1t}$$

Where,

Q = the amount of drug release at time t,

K1= first order release constant

The plot made: log cumulative of % drug remaining vs. time (first order kinetic model).

Higuchi Square Root of Time Equation

Many controlled-release products are designed on the principle of embedding the drug in a porous matrix. Liquid penetrates the matrix and dissolves

the drug, which then diffuses into the exterior liquid. Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion. Release rate from both a planar surface and a sphere was considered. The analysis suggested that in the case of spherical pellets, the time required to release 50% of the drug was normally expected to be 10% of the time required to dissolve the last trace of solid drug in the center of the pellet. Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

$$Q = Kt^{1/2}$$

Where, **Q** = the amount of drug release at time t,

K = the Higuchi square root of time release constant.

Korsmeyer and Peppas Release Mechanism

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$\frac{M_t}{M_\alpha} = Kt^n$$

Log (Mt/Mα) = Log K + n Log t

Where, **Mt/Mα** is the fractional drug release at time t

K is a kinetic constant incorporating structural and geometrical

Characteristic of the drug/polymer system (devices).

n is diffusion exponents that characterizes the mechanism of drug release,

t is the time.

Table 2: n value showing different release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	(Non-Fickian) Anomalous diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Skin irritation study

For skin irritation study animals were used under protocol CPCSEA/VBT/IAEC/14/01/68 given by Institute animal ethical committee.

Animals to be required

1. Species/ Common name : Wistar rats
2. Weight : 150-200 grams
3. Gender : Male
4. Number to be used : 18

Groups	Route of drug administration	No. of Animals
Control	Topical route	**6**
Standard (Transdermal patch of without drug)	Topical route	**6**
Transdermal patch of with drug	Topical route	**6**

Procedure:

Skin irritation and sensitization testing can be performed on healthy wister albino rats. The rats were divided into three groups of six rats in each group.

The dorsal surface ($4cm^2$) of the rats were cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin was observed and classified into 5 grades on the basis of the severity of skin injury.

Stability study (As per ICH guidelines)

Stability studies were carried out for optimized patch formulation at 40 ± 0.5°C and 75 ± 5% RH for 1 month. The samples were withdrawn at 0, 10, 20, 30 days and evaluated for physicochemical properties and *in*-vitro diffusion study

Drug polymer compatibility

Fourier transformer infrared spectroscopy

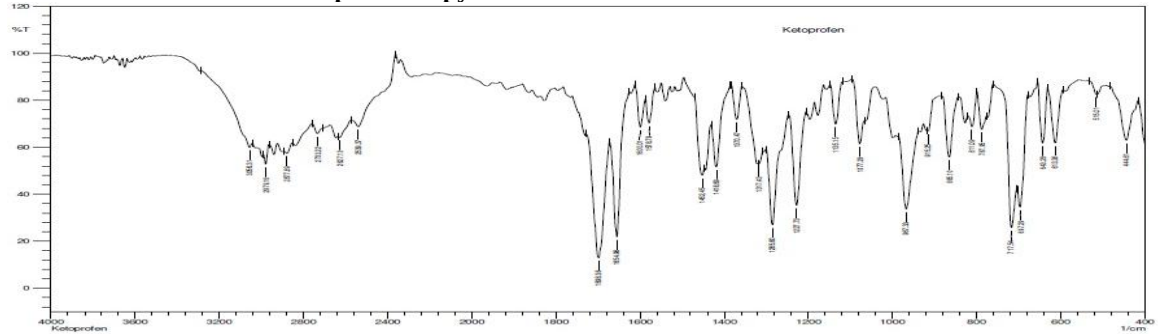

Fig 1: IR Spectrum of Ketoprofen

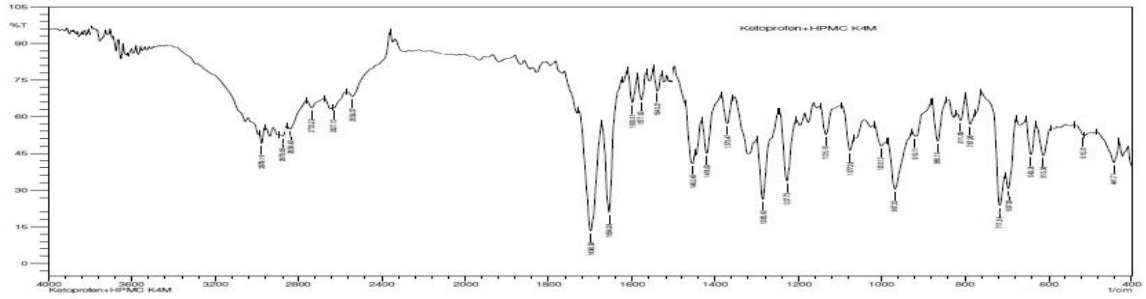

Fig 2: IR Spectrum of Ketoprofen and HPMC k_4M

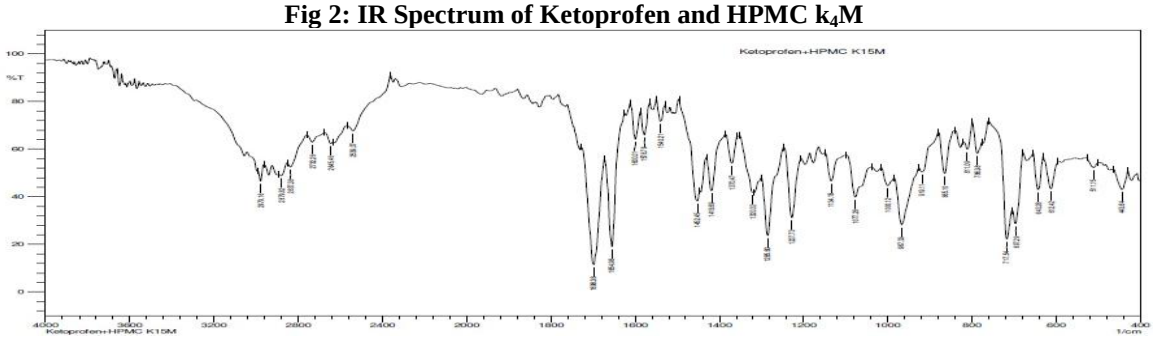

Fig 3: IR Spectrum of Ketoprofen and HPMC $k_{15}M$

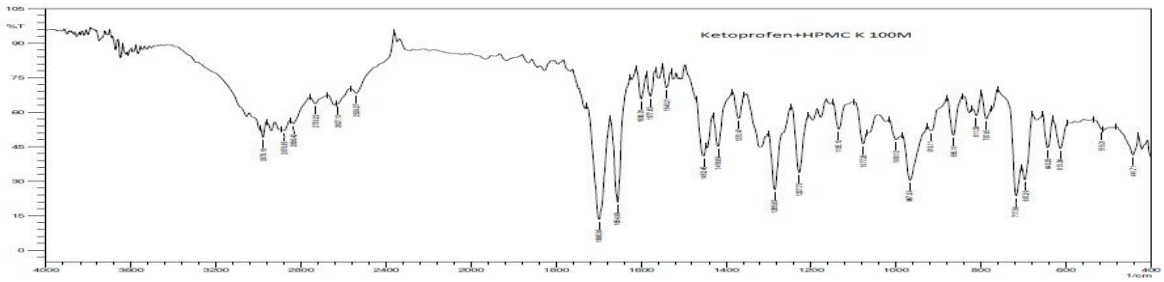

Fig 4: IR Spectrum of Ketoprofen and HPMC $k_{100}M$

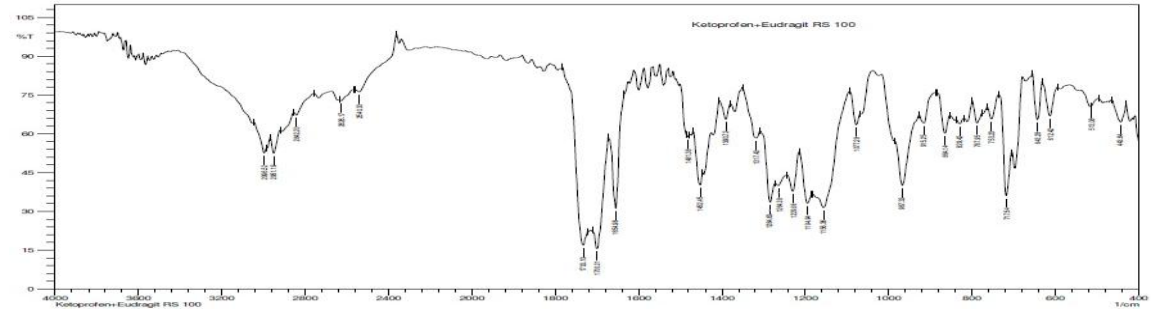

Fig 5: IR Spectrum of Ketoprofen and Eudragit RS-100

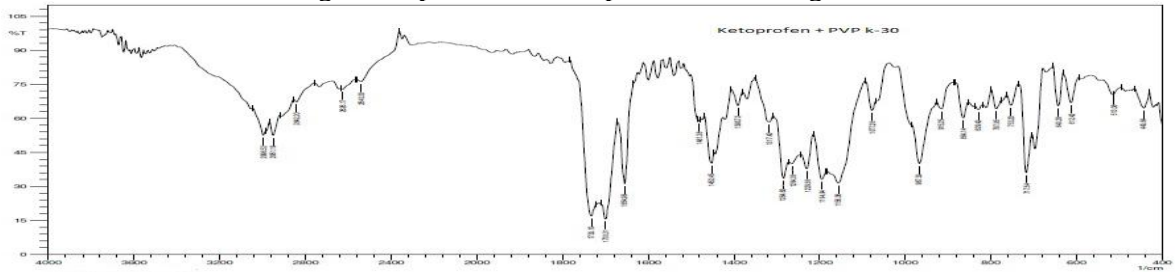

Fig 6: IR Spectrum of Ketoprofen and PVP K-30

All characteristic peaks of pure drug Ketoprofen, and it's with HPMC K-4, HPMC K-15, HPMC K-100, PVP K-30 and Eudragit RS-100 mentioned above are not seem to be, affected in FTIR spectra of physical mixture, although intensity changed due to change in proportion of drug in physical mixture. There was overlapping of the spectras of Ketoprofen and spectra physical mixture of

Ketoprofen and Polymer mixture (1:1) indicating that there was no interaction between Ketoprofen and HPMC K-4, HPMC K-15, HPMC K-100, PVP K-30 and Eudragit RS-100, which indicated no incompatibility of drug with polymers.

Determination of Partition co-efficient

Table 3: Partition co-efficient of Ketoprofen

Drug	Actual value	Observed value (n=3)
Ketoprofen	3.12	3.17 ± 0.015

Aqueous solubility and lipophilicity have been shown to influence Membrane flux, therapeutic activity, and pharmacokinetic profiles of drugs. Lipophilicity is essential for transdermal penetration because the stratum corneum, the major barrier to drug permeation, is lipophilic and, in general, favours permeation by lipophilic drugs. Determination of the log P can be used to evaluate the lipophilicity of the drug. The log P value for Ketoprofen was 3.17 ± 0.015.This value indicates that Ketoprofen possesses an appropriate lipophilicity for skin permeation.

Preliminary solvent selection and Optimization of Plasticizer concentration

Preliminary solvent selection

Preliminary formulation and plasticizer optimization:

Table 4: Preliminary solvent system

Code	Solvents	Ratio
1	Methanol: Dichloromethane	1:1
2	Methanol: Dichloromethane	1:2
3	Methanol:Chlorofoam	1:1
4	**Methanol:Water**	**1:1**

Transdermal patches were prepared with HPMC various grades with PVP K-30 and Eudragit RS-100 using different casting solvents like 1) Methanol: Dichloromethane 2) Methanol: Chloroform and 3) Methanol: Water systems. Obtaining films of HPMC and PVP K 30 were evaluated for different physical property in terms of clarity, frothing, smoothness. Film prepared with first solvent system (1) showed more and more entrapped air bubble so poor appearance because of rapid evaporation of solvent. Film prepared with Second solvent system (2) showed film with white spot because polymer not fully dissolved in (2) solvent system. Film prepared with third solvent system (3) showed clear film without any air bubble and also showed good elasticity and strength. So this solvent system was selected for further study.

Table 5: Preliminary formulation

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K_4M (mg)	100	200	200	300	300	-	-	-	-
HPMC $K_{15}M$ (mg)	-	-	-	-	-	300		-	-
HPMC $K_{100}M$ (mg)	-	-	-	-	-	-	300	-	-
Eudragit RS 100 (mg)	-	-	-	-	-	-	-	300	-
PVP K-30 (mg)	-	-	-	-	-	-	-	-	300
PEG-400	15%	15%	20%	15%	20%	20%	20%	20%	20%
DMSO	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%
Solvent (Methanol: Water)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Total	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml
Result	No film formation	Very thin, Brittle	Very thin, Flexible	Thin less flexible	Thin, Transparentflexible good elasticity	Thin, Transparent,flexiblegood elasticity	Thin, Transparent,flexible good elasticity	Thin, Transparent,flexible good elasticity	No film formation

Average petri plate size=21.2 cm^2

From the preliminary formulation it can be find out at which concentration of polymer and plasticizer, the transdermal film forms. Hence the polymeric blend produces a more controlled release due to cross-linking structure in nature.

Table 6: Preliminary screening of polymeric blend of HPMC K-4: PVP K-30

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K_4M+ PVP k-30	1:2	1:4	1:8	**2:3**	2:5	2:7	2:9	**3:2**	3.5
PEG-400	20%	20%	20%	**20%**	20%	20%	20%	**20%**	20%
DMSO	0.6%	0.6%	0.6%	**0.6%**	0.6%	0.6%	0.6%	**0.6%**	0.6%
Solvent (methanol: water)	1:1	1:1	1:1	**1:1**	1:1	1:1	1:1	**1:1**	1:1
Total	20ml	20ml	20ml	**20ml**	20ml	20ml	20ml	**20ml**	20ml
Result	Very thin, Transparent, Uneven and Good elasticity	Very thin, Transparent, Uneve, Sticky and Good elastic	No film formation	**Thin, Transparent,Uniform, flexible and good elasticity**	Thin, Transparent, Uniform, Sticky and Good elasticity	Thin, Transparent, Uniform Sticky and Very elastic	Thin, Transparent, Uniform Very sticky and Very elastic	**Thin, Transparent Uniform, flexible and good elasticity**	Thin, Transparent, Uniform Sticky and Good elastic

Average petri plate size=21.2 cm^2 **&** Total amount of Polymer incorporated =300 mg

From the preliminary screening of polymeric grade HPMC K-4: PVP K-30 in a ratio of 2:3 and 3:2 shows a transparent and flexible and good elastic polymeric patch and the lower viscosity polymer produces a relatively more transdermal patch and The batch F4 and F8 batches are carried out for further study.

Table 7: Preliminary screening of polymeric blend of HPMC K-15:PVP K-30

Batch code	F10	F11	F12	F13	F14	F15	F16	F17	F18
HPMC $K_{15}M$+ PVP k-30	1:2	1:4	1:8	**2:3**	2:5	2:7	2:9	**3:2**	3.5
PEG-400	20%	20%	20%	**20%**	20%	20%	20%	**20%**	20%
DMSO	0.6%	0.6%	0.6%	**0.6%**	0.6%	0.6%	0.6%	**0.6%**	0.6%
Solvent (methanol:water)	1:1	1:1	1:1	**1:1**	1:1	1:1	1:1	**1:1**	1:1
Total	20ml	20ml	20ml	**20ml**	20ml	20ml	20ml	**20ml**	20ml
Result	Thin, Transparent, Uneven and Good elastic	Thin, Transparent, Uniform, Sticky and Good elastic	No film formation	**Thin, Transparent, Uniform, flexible and good elasticity**	Thin, Transparent, Uniform, Sticky and Very elastic	Thin, Transparent, Uniform, Very sticky and Good elasticity	Thin, Transparent, Uniform, Very sticky and Very elastic	**Thin, Transparent, Uniform, flexible and good elasticity**	Thin, Transparent, Uniform and Good elastic

Average petri plate size=21.2 cm^2 **&** Total amount of Polymer incorporated =300 mg

From the preliminary screening of polymeric grade HPMC K-15:PVP K-30 in a ratio of 2:3 and 3:2 shows a *transparent and flexible and good elastic polymeric patch and the lower viscosity polymer produces a relatively more transdermal patch and The batch F13 and F17 batches are carried out for further study.*

Table 8: Preliminary screening of polymeric blend of HPMC K-100:PVP K-30

Batch code	F19	F20	F21	F22	F23	F24	F25	F26	F27
HPMC $K_{100}M$+ PVP k-30	1:2	1:4	1:8	**2:3**	2:5	2:7	2:9	**3:2**	3.5
PEG-400	20%	20%	20%	**20%**	20%	20%	20%	**20%**	20%
DMSO	0.6%	0.6%	0.6%	**0.6%**	0.6%	0.6%	0.6%	**0.6%**	0.6%
Solvent (Methanol : Water)	1:1	1:1	1:1	**1:1**	1:1	1:1	1:1	**1:1**	1:1
Total	20ml	20ml	20ml	**20ml**	20ml	20ml	20ml	**20ml**	20ml
Result	Thin, Transparent, Uneven and Good elastic	Thin, Transparent, Uneven Sticky and Very elastic	No film formation	**Thin, Transparent, Uniform, flexible and good elasticity**	Thin, Transparent, Uniform and Good elastic	Thin, Transparent, Sticky and Very elastic	Thin, Transparent, Very sticky and Very elastic	**Thin, Transparent, Uniform, flexible and good elasticity**	Thin, Transparent, Uniform and Good elastic

From the preliminary screening of polymeric grade HPMC K-100: PVP K-30 in a ratio of 2:3 and 3:2 shows a transparent and flexible and good elastic polymeric patch and the lower viscosity polymer produces a relatively more transdermal patch and The batch F22 and F26 batches are carried out for further study.

Table 9: Preliminary screening of polymeric blend (Eudragit RS-100:PVP K-30)

Batch code	F28	F29	F30	F31	F32	F33	F34	F35	F36
Eudragit RS 100+ PVP k-30	1:2	1:4	1:8	**2:3**	2:5	2:7	2:9	**3:2**	3.5
PEG-400	20%	20%	20%	**20%**	20%	20%	20%	**20%**	20%
DMSO	0.6%	0.6%	0.6%	**0.6%**	0.6%	0.6%	0.6%	**0.6%**	0.6%
Solvent (methanol:water)	1:1	1:1	1:1	**1:1**	1:1	1:1	1:1	**1:1**	1:1
Total	20ml	20ml	20ml	**20ml**	20ml	20ml	20ml	**20ml**	20ml
Result	Thin, Transparent, Uneven and Good elastic	Thin, Transparent, Uneven Sticky and Very elastic	No film formation	**Thin, Transparent, Uniform, flexible and good elasticity**	Thin, Transparent, Uniform and Good elasticity	Thin, Transparent, Sticky and Very elastic	Thin, Opaque, Very sticky and Very elastic	**Thin, Transparent, Uniform, flexible and good elasticity**	Thin, Opaque, Uniform, flexible and Good elasticity

Average petri plate size=21.2 cm^2 & Total amount of Polymer incorporated =300 mg

From the preliminary screening of polymeric grade Eudragit RS-100: PVP K-30 in a ratio of 2:3 and 3:2 shows a transparent and flexible and good elastic polymeric patch and the lower viscosity polymer produces a relatively less transdermal patch than HPMC hydrophilic polymer and The batch F31 and F35 batches are carried out for further study. So it can be concluded that the ratio of 2:3 and 3:2 for various polymeric blend was found to be best suitable for the formulation on the basis of the physicochemical properties. Batch no F4, F8, F13, F17, F22, F26, F31 and F35 was carried out for the further study. HPMC AND Eudragit were selected on the basis of their adhering and non toxicity.

Dose of drug and loading dose calculation

Dose of drug = $\frac{\text{Oral Dose of drug} \times \text{Oral bioavability}}{\text{Body surafa ce area}}$

Where, oral dose of drug (Ketoprofen) =100 mg
Oral bioavability = 70%
Body surface area = 1.73 m^2
=40 mg dose

Drug loading calculation

Average patch size=21.2 cm^2
Dose of Drug (Ketoprofen)=40 mg
4 cm^2 (2 cm*2 cm) of patch stripe=40 mg of drug (Ketoprofen)
21.2 cm^2 of petri plate size= (?)

$= \frac{40 * 21.2}{4}$

= 212 mg of Ketoprofen in 21.2 cm^2 petri plate

Dose of drug (Ketoprofen) was 40 mg to provide a effective therapeutic treatment.

Batch design

Table 10: Batch design using four polymer blends with 2:3 and 3:2 ratio

Code	Drug (mg)	HPMC k_4M +PVP K-30 (mg)	HPMC $k_{15}M$ + PVP K-30 (mg)	HPMC $k_{100}M$+ PVP K-30 (mg)	Eudragit RS-100 + PVP K-30 (mg)	PEG -400	DMSO	SOLVENT	TOTAL
F-1	40	2:3	-	-	-	20%	0.6%	1:1	20ml
F-2	40	3:2	-	-	-	20%	0.6%	1:1	20ml
F-3	40	-	2:3	-	-	20%	0.6%	1:1	20ml
F-4	40	-	3:2	-	-	20%	0.6%	1:1	20ml
F-5	40	-	-	2:3	-	20%	0.6%	1:1	20ml
F-6	40	-	-	3:2	-	20%	0.6%	1:1	20ml
F-7	40	-	-	-	2:3	20%	0.6%	1:1	20ml
F-8	40	-	-	-	3:2	20%	0.6%	1:1	20ml

From the experiment it was concluded that transdermal patch of HPMC:PVP polymers are relatively more transparent than Eudragit :PVP due to less water permeability of Eudragit to water.

Characterization of Developed Transdermal patch:

Table11:Physico-chemical evaluation

Batch Code	Parameters				
	Thickness (mm) ± S.D	Weight uniformity (gm) ± S.D	Drug Content (%) ± S.D	Folding Endurance ± S.D	Flatness (%)
F-1	0.26±0.029	0.224 ± 0.082	92.3± 0.090	64 ±0.654	94±0.765
F-2	0.28±0.033	0.289 ± 0.098	94.7±0.078	72±0.765	92±0.876
F-3	0.25±0.036	0.321± 0.076	95.3±0.065	68±0.565	95±0.654
F-4	0.27±0.025	0.375± 0.067	97.7±0.098	73±0.765	94±0.676
F-5	0.19±0.027	0.458± 0.090	94.2±0.068	76±0.987	97±0.876
F-6	0.23±0.027	0.472± 0102	95.6±0.065	84±0.876	95±0.676
F-7	0.26±0.029	0.343± 0.089	92.4±0.076	79±0.546	98±0.564
F-8	0.23±0.029	0.398± 0.084	94.6±0.087	94±0.765	99±0.765

The prepared transdermal patches were evaluated for their physico-chemical properties like physical appearance, weight uniformity, Drug content, folding endurance and flateness. The physical appearance of the various formulations were uniform, transparent, smooth and flexible in nature. The transparencies of HPMC polymeric patch were more than Eudragit due to less water permeability of eudragit.

Thickness: The thickness of the patches varies between 0.19±0.029 to 0.28±0.027. Low standard deviation values shows uniformity of the patches prepared by solvent casting method. As the viscosity of polymer increases, the thickness also increases due to weak hydrogen bonding with water molecule.

Drug content: Drug content was found to be 92.3% to 97.7%. From the result it can be concluded that as the amount of low viscosity hydrophilic polymer concentration increases, the drug content also increases due to relatively weak hydrogen bonding between the polymeric molecule form a less cross-linking matrix structure.

Folding endurance: Folding endurance shows the mechanical streangth to with stand with the condition.

Tensile Strength and % Elongation

Table 12: Tensile Strength and % Elongation

Batch Code	Parameters	
	Tensile strength (kg/cm^2) ± S.D	Percentage elongation break test (%) ± S.D
F-1	2.2± 0.123	17.78±0.032
F-2	2.4±0.143	19.08±0.043
F-3	2.6±0.149	15.45±0.042
F-4	2.9±0.243	18.56±0.056
F-5	3.4±0.213	14.43±0.076
F-6	3.8±0.234	12.78±0.086
F-7	4.4±0.214	17.12±0.076
F-8	4.5±0.217	18.98±0.065

From the result it can be concluded that as viscosities increases tensile strength also increases. It varies from 2.2 to 3.8 kg/cm^2.This may be due to hydrogen bonding that more cross-linked with increases in viscosities of the polymer grade. Tensile strength shows the mechanical strength to protects the formulation.

% Percentage elongation also depends on the hydrogen bonding of polymer molecule to water molecule. As the lower viscosity polymer shows more elongation.

Moisture uptake and moisture content

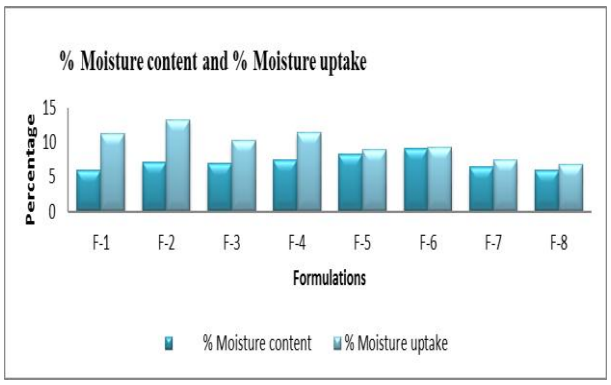

Fig 7: Graph of moisture uptake and content of polymeric blend

The result signified that the polymeric patches prepared with hydrophilic polymer shows more moisture uptake. The batch F1 to F6 had shown more moisture uptake and slow moisture content. As the concentration of hydrophilic polymer increases it also increases the moisture uptake. Since small moisture loss helps the patch to remain stable, brittle and free from complete drying. Generally the HPMC polymer posses the 10-12% moisture in there structure.

Adhesive study evaluation

Shear adhesion test

Table 13: Shear adhesion test

Sr.no	Applied weight (mg)	Residual time (min)	Cohesive strength
1	100	32 min	Excellent
2	200	23 min	Excellent
3	300	17 min	Good

Transdermal patch requires the physibility of the patches to apply the dosage form for certain period of time for effective treatment. The result had shown to decrease the residual time as the applied weight increases. The cohesive strength of the adhesive material depends upon the cross linking structure of the molecule.

***In*-vitro permeation study (By Franz-diffusion cell)**

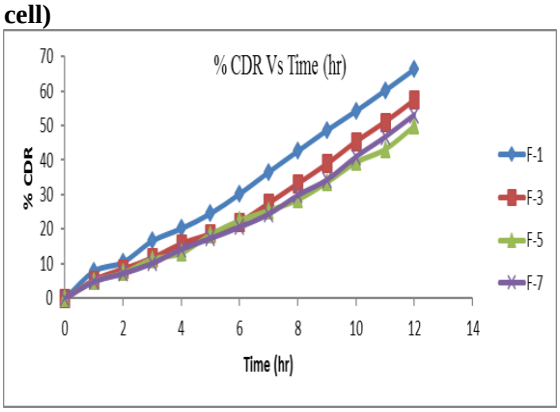

Fig: 8 Graph of %CDR VS Time of F1, F3, F5, and F7 of 2:3 ratio

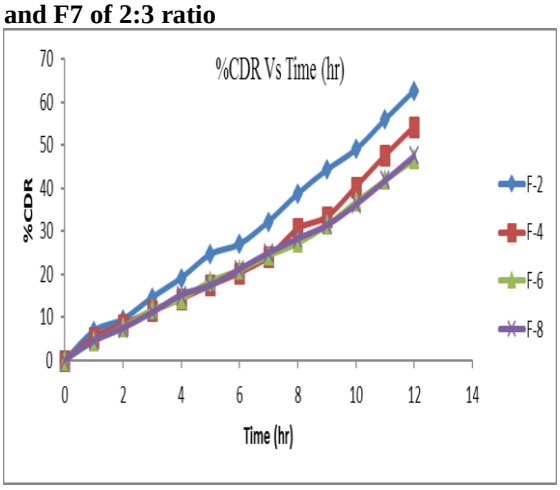

Fig: 9 Graph of %CDR VS Time of F2, F4, F6, and F8 of 3:2 ratio

Release studies are required for predicting the reproducibility of the rate and duration of drug release. The result indicated the release of the drug increases with increases the concentration of the hydrophilic polymers. The cumulative percentage of drug release in 12 hours was found to be highest in F1 (66.37%) but F1 batch shows more control and extent of drug release.

Flux and permeability co-efficient

Table 14: Flux and permeability co-efficient.

Time (hrs)	Batch F1	
	Flux *J* (mg/cm^2/hr) ± S.D	Permeability co-efficient (k_p) ± S.D
0	0	0
1	1.982±0.019	0.165±0.065
2	1.313±0.026	0.109±0.054
3	1.387±0.018	0.115±0.063
4	1.265±0.014	0.105±0.054
5	1.231±0.012	0.103±0.057
6	1.261±0.011	0.105±0.042
7	1.333±0.016	0.111±0.074
8	1.356±0.015	0.113±0.064
9	1.382±0.019	0.115±0.054
10	1.135±0.017	0.113±0.073
11	1.386±0.014	0.114±0.043
12	1.382±0.011	0.115±0.049

From the result it was concluded that F1 shows more controlled release at an extent. It helps to provide minimum effective concentration.The cumulative amount of drug permeated was fitted to the Zero, First, Hixson-Crowell, Krosmeyer-Peppas, Hiquchi equation. n value of krosmeyer-peppas nearer to 0.5 shows that the release profile of the optimized F1 batch indicates that non-fickianian anomolus mechanism.

Scanning Electron Microscopy studies (SEM) of F1 optimized batch

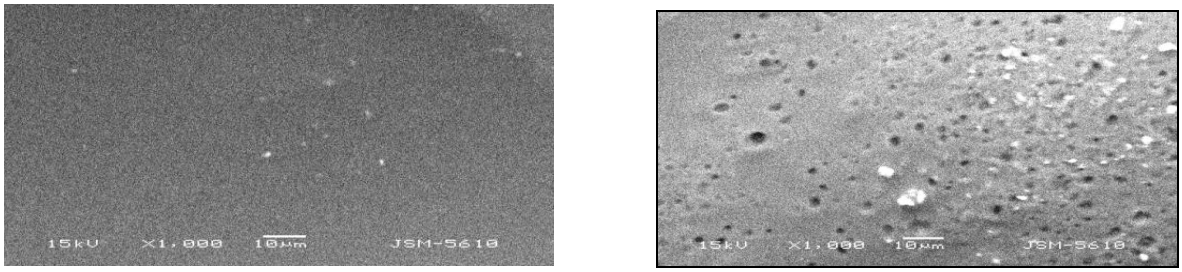

Fig 10: Scanning Electron Microscopy studies

a) SEM of Transdermal patch without drug **b) Transdermal patch with drug**

From the sem study it was concluded that the drug loaded patch shows more porous nature which helps to release the drug after swelling by slowing erosion mechanism.

Skin irritation study

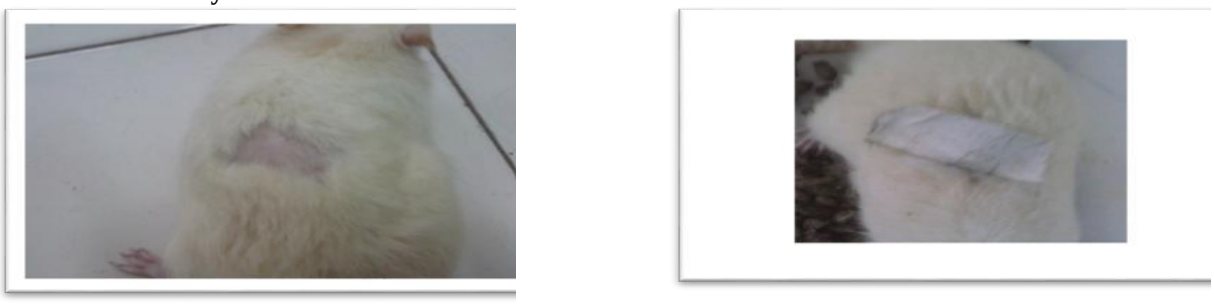

Fig 11: Observation after 48 hrs

(2) Patch secured with adhesive tape

Group		Score For Erythema		
		After 4hr	After 24hr	After 48 hr
Normal	1	0	0	0
	2	0	0	0
	3	0	0	0
Control (patch without drug)	1	0	0	0
	2	0	0	0
	3	0	0	0
Test (Drug loaded patch)	1	0	0	0
	2	0	0	0
	3	0	0	0
		Score For Edema		
Normal	1	0	0	0
	2	0	0	0
	3	0	0	0
Control (patch without drug)	1	0	0	0
	2	0	0	0
	3	0	0	0
Test (Drug loaded patch)	1	0	0	0
	2	0	0	0
	3	0	0	0

Stability Study (As per ICH guidelines) Stability study of optimized batch F1 (initial one month stability study) [27-29].

After the one month stability study of optimized formulations F3, values of all physic-chemical parameters like appearance, thickness ,Tensile strength were almost similar to the initial values. The % drug release and diffusion profile was just a same of the initial profile. There were not any significant changes in any values so the formulation was stable and able to provide a effective therapy for long term therapeutic uses.

CONCLUSION:

Long term oral administration of Ketoprofen generally results in low bioavailability due to its short half life (1.5-2 hours). By development of transdermal matrix patch of Ketoprofen using HPMC and PVP K 30 and Eudragit RS-100 and PVP K-30 as release controlling polymers and methanol: water (1:1) as solvent, increases permeability and bioavailability of ketoprofen and increase patient compliance. All the formulations showed acceptable physiochemical characteristics i.e. appearance, thickness, folding endurance, moisture content. From the identification tests such as Ultra violet visible spectroscopy, Infrared spectroscopic study, melting point, partition co-efficient it was conclude that drug sample is Ketoprofen with acceptable purity grade. Partition coefficient Value shows that Ketoprofen possess the sufficient lipophilicity.The biphasic nature of Ketoprofen mimic the biphasic nature of skin thus it can easily penetrate through the skin. A low concentration of Plasticizer gives a rigid and brittle polymeric film. So plasticizer is required to improve mechanical property. HPMC and Eudragit rs-100 both are hydrophilic polymers in nature. As the molecular weight of polymer increases the viscosity also increases. Swelling index is considered in hydrophilic nature of Ketoprofen. Since HPMC K_4M: PVP K-30 shows the higher swelling index as it contains a weak physical bonds in a polymeric chain. Elasticity and elongation is more in HPMC higher percentage than Eudragit. *In*-vitro permeation study shows that the formulation of F-1 batch with HPMC K-4 M: PVP K-30 shows more sustained release of drug during 12 hrs study.

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